Drug Information and Determination Sheet

Is it a Drug?

• Is it intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease?
  ○ If yes, this is a drug and subject to the regulations.

• Is it a substance (other than food) used to affect the structure or any function of the body?
  ○ If yes, this is a drug and subject to the regulations.

• Will it blunt or provoke a physiological reaction?
  ○ If yes, this is a drug and subject to the regulations.

• Is it looking at the mechanism of action or metabolism of the drug?
  ○ If yes, this is a drug and subject to the regulations.

Is it an Investigational Drug?

• Is the drug used in a clinical investigation?
  ○ If yes, this drug is subject to the regulations and needs an IND.

• Is the drug lawfully marketed in the U.S, but NOT BEING USED IN ACCORDANCE WITH ITS LABEL?
  ○ If yes, this drug is subject to the regulations and needs an IND.

Is it Lawfully Marketed in the U.S?

• Is it Commercially Available?
  ○ If no, this needs an IND

• Is it Legally Marketed (marketed in manner congruent with labeling)
  ○ If no, this needs an IND

Is it used on or off label?

• On Label: Used in accordance with approved label and it is used in the same indication, same dose, same route of administration, same patient population, same drug formulation, same drug combinations.
  ○ If no, this drug is subject to the regulations and needs an IND.
  ○ If the data from this study is used in a marketing application or to change advertising – then it will need an IND

• Off Label: There is a difference in how the drug is used from when it was approved for use. This includes drug combinations (combined with other drug products not described in the label)
  ○ If yes, this drug is subject to the regulations and needs an IND.
  ○ Note: Off label use is common in clinic practice and it can be a standard of care – and a doctor can use it off label in this manner and then publish on those results etc, but the drug manufacturer may never update their application. Though this use is off label and can be standard of care, the study would be subject to an IND if it’s done for clinical investigation and it is considered off label use.
Does this Drug qualify for an Exemption?

- Is it an investigation of a drug product that is lawfully marketed in the U.S?
  - Answer must be yes. If yes, then proceed to the following criteria.

- Does the drug meet these 5 criteria, if yes, it qualifies for exemption.
  - The study is NOT DESIGNED to support approval of a new indication or change in label
    - If yes, it qualifies for exemption.
  
  - The study is NOT INTENDED to support a significant change in the advertising for the product.
    - If yes, it qualifies for exemption.

  - The study DOES NOT INVOLVE a route of administration, dosage level, patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.
    - If yes, it qualifies for exemption.

  - The study is conducted in compliance with the IRB and Informed Consent regulations.
    - If yes, it qualifies for exemption.

  - The study is conducted in compliance with regulations regarding promotion for investigational drugs.
    - If yes, it qualifies for exemption.

Note: Research with Non-Commercial Intent may also require an IND and regulations apply regardless if there is an intent to commercialize a product.
IND Exemption 21CFR 312.2(b) – Criteria:

- Is it an investigation of a drug product that is lawfully marketed in the U.S? – Answer must be yes.

- If it meets the above, then these 5 criteria must be met for an IND Exemption
  - The study is NOT DESIGNED to support approval of a new indication or change in label
  - The study is NOT INTENDED to support a significant change in the advertising for the product.
  - The study DOES NOT INVOLVE a route of administration, dosage level, patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.
  - The study is conducted in compliance with the IRB and Informed Consent regulations.
  - The study is conducted in compliance with regulations regarding promotion for investigational drugs.
  - Note: The exemption provision was not intended to require use of only the marketed product. Sponsor-investigators can make low risk modifications to the lawfully marketed drug (ex: over-encapsulation, changes to color, scoring or size for blinding purposes) – Consult FDA and provide detailed manufacturing information such that a determination can be made.
  - Note: Though you can (for a lot of reasons), you do not have to go to the FDA to get an IND Exemption. You can consult them, but you are not required to go to them to get an IND Exemption. The investigator is best positioned to make this risk assessment. Investigator must make the initial determination.
    - Investigator submits rationale to IRB
    - IRB makes determination.
      - If the IRB agreed that no IND is needed, it is conducted with just IRB oversight.
      - If IRB does not agree, then it goes to the FDA

- Formal Process for IND Exemption with FDA:
  - 30 day time-clock once submitted
    - Submit cover letter, IND document, Protocol, Consent, Forms 1571, 1572, 3674, Letters of Authorization (if applicable) and reprints form the literature (2-3 references)
  - If exempt, FDA gives official letter
  - If not exempt, you will have an active IND – unless changes are required etc for a full IND.

- Informal Process for IND Exemption with FDA:
  - Reach out to FDA review division
  - Less work, may get faster response
  - Not official letter, may be in writing or verbally over phone.

- Contact the appropriate FDA Review Division
  - Center for Drug Evaluation and Research (CDER)
  - Center for Biologics Evaluation and Research (CBER)
  - Then select office/areas within CDER or CBER
Is an IND Needed?

- When INDs are needed, PI's must discuss the risks associated with: Population, route of administration, dosage, drug combinations, drug modifications, use of placebo
- Authorization must be secured before interstate/international shipment of drug
- Examples:
  - Clinical investigations using a product that is not lawfully marketed in the US as a drug, need an IND
  - Using a test article that is NOT legally marketed in the US as a drug in a clinical investigation – Requires and IND
  - Using a test article that IS legally marketed in the US as a drug in a clinical investigation – May or May not require an IND
- Suggest having a Pre-IND meeting with FDA if an IND is needed – Not Required.
  - Have the meeting before making major manufacturing and preclinical decisions.
  - Can only have one meeting per application.
  - There should be a meeting briefing package

Preparing and Submitting your IND Application to the FDA and Maintenance of IND

- Definitions:
  - Sponsor: An individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation.
  - Investigator: An individual who conducts a clinical trial, i.e. under whose immediate direction a drug is administered or dispensed.
  - Sponsor-Investigator: An individual who both initiates and conducts an investigation, and under whose immediate direction a drug is administered or dispensed.
- Two Types of INDs:
  - Commercial IND: ultimate goal is to obtain marketing approval
  - Sponsor-Investigator IND: Investigator initiated the IND, it’s primarily research driven and the goal is publication.
- Form and Content for an IND: Form 1571 (cover sheet), table of contents, intro statement, general investigation plan, investigator’s brochure, protocols, chemistry, manufacturing and control data, pharmacology and toxicology data, previous human experience, additional information, biosimilar user fee cover sheet, clinical trials certificate of compliance (form 3674).
- 30 day review clock for the FDA once it is submitted
  - IND goes into effect 30 days after the FDA receives the IND – unless the FDA notifies the sponsor/investigators otherwise.
  - FDA may notify sponsors/investigators earlier.
  - Can legally begin your study once IRB is approved but you should wait to confirm with the FDA.
  - If issues with application – the FDA will contact investigators and sponsors
- Maintenance of IND
  - Protocol Amendments: IND submission that contains new or updated information.
    - Includes new protocols, change in protocols, new investigators, and marketing protocols. Submit before all changes are implemented.
    - FDA only replies if they have concerns about it.
    - INDs can contain multiple protocols if covers same drug and similar indication.
- In emergency – intended to eliminate an apparent immediate hazard to humans – may be implemented immediately and the FDA and IRB is notified by the change afterward.
**Endogenous Compounds**: naturally found in the body, often used in challenge studies to evoke physiological response, characterize a disease, or establish a mechanism of action. These studies require an IND.

**Live Organisms**: viruses, bacteria, and fungi – often used in challenge studies and are administered to study pathogenesis or host response. These require an IND because these re not lawfully marketed drugs.

**Dietary Supplements**: products taken by mouth that are intended to supplement the diet and contain a dietary ingredient. Examples are vitamins, minerals, herbs, botanicals, amino acid, metabolites, including extracts of combinations of these things. For IND regulations – these are seen more as a food.

- Need for an IND is determined by intent of the study using the dietary supplement.
- If the intent is to look at structure or functional changes in the body – no IND is required.
  - Ex: calcium on bone mass or fiber on bowel regularity – not looking to treat a disease.
- If the dietary supplement is intended to be used in therapeutic studies with the intent to treat, diagnose, cure, mitigate etc, then an IND is required.
  - Ex: calcium on osteoporosis prevention or fiber to treat diarrhea.

**Tobacco Products**: Any product that is made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product. Includes electronic nicotine delivery systems.

- Regulated as drugs under 2 circumstances and need IND:
  - The product is intended for use in the diagnosis of disease or other conditions, in the cure, mitigation, treatment or prevention of disease.
    - Ex: cure nicotine addiction – like cessation studies, relapse prevention, or relief of nicotine withdrawal symptoms
  - The product is intended to affect the structure or any function of the body in a way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to 3/21/2000.
    - Ex: structure/function claims that were commonly and legally claimed before 3/21/2000 include satisfaction (including addiction), pleasure, enjoyment, and refreshment. So if a study is conducted at whether subjects experience pleasure or enjoyment of a tobacco product – then it does not need an IND.

- Tobacco product studies that do not require an IND can be submitted to the FDA in an Investigational Tobacco Product Application (this is not mandatory). Ex: assessing smoker preference of cigarettes of varying nicotine level.

**Research with Non-Commercial Intent**: IND regulations apply regardless if there is an intent to commercialize a product.